REMARKS

Applicants believe the Title is descriptive of the instant invention and therefore have not amended it

The "Brief description of the drawings" has been amended as suggested by the Examiner, to clarify the sequences to which SEQ ID NOs apply.

Applicants disagree that the terms "improved affinity to said ED-B epitope," "characteristic epitope," and "capable of" render the claims indefinite. Nevertheless, in an effort to expedite prosecution, the claims have been amended to clarify their meaning. The scope of the claims is unaltered.

The term "ED-B" has not been amended. This term is an art-recognized term denoting this oncofetal domain of fibronectin. One of skill in the art would recognize this term without the need of further explanation.

New claims have been added which recite, *e.g.*, that the affinity of the antibody for the ED-B domain is "in the subnanomolar range" (*e.g.*, claims 28-32 and 37-38) or that the affinity is about 0.05 nM (*e.g.*, claim 39). Support for the recitation of "subnanomolar affinity" is found in the specification, *e.g.*, at page 1, lines 5-6 and at page 5, lines 1-3. An antibody which is exemplified in the specification - antibody L19 - exhibits a K_d of only 0.054 nM, within the recited range of "in the subnanomolar range."

A PTO-892 Form was not provided with the Office Action of September 26, 2000. Applicants assume that the Mariani reference cited in that Office Action is the same as the reference cited in related application 09/075,338 [Mariani *et al.* (Dec. 15, 1997). *Cancer* 80 (12 Supp.), 2484-9]. Confirmation is requested, as well as a PTO-892 form indicating all of the references which were cited in the September 26, 2000 Office Action.

The Mariani reference does not anticipate the instant claims. Mariani is drawn to the "BC-1" antibody, which recognizes domain 7 of fibronectin (which is adjacent to the ED-B domain), not the ED-B domain. As is noted in the instant specification, for example at page 4, lines 1-5, with regard to the BC-1 antibody (which is also discussed in Carnemolla *et al.* 1992, *J. Biol. Chem.* 267, 24689-92), "the BC1 antibody ... recognizes an epitope on domain 7 of FN [fibronectin], but not on the ED-B domain, which is cryptic in the presence of the ED-B domain of fibronectin. ... Therefore, the BC-1 antibody and the antibodies of the present

invention show different reactivity." BC-1 is clearly different from the instantly claimed antibody, and thus does not anticipate it.

The Neri reference does not anticipate the instant claims, at least because the reference does not disclose an antibody which exhibits "high affinity" for the ED-B domain. In support of the allegation that Neri discloses such "high affinity," the Examiner refers to claim 14 therein; however, claim 14 recites that the antibody has a dissociation constant of "$6x10^{-8}$M [*i.e.*, $60x10^{-9}$M] or less for ED-B FN." $6x10^{-8}$M is clearly not "high affinity," and certainly is not in the "subnanomolar range" recited in, *e.g.*, instant claims 28- 32. Although the CGS-2 antibody of Neri is shown in Table 1 to exhibit a K_d of 1.1 nM, this does not qualify as "subnanomolar." The reference does not disclose all the material elements of the claims (*e.g.*, a "high affinity" antibody or one in which the affinity is in the "subnanomolar range") and therefore is not anticipatory.

The two Thorpe references not do anticipate the instant claims, at least because they do not disclose an antibody specific for ED-B. At best, they disclose an antibody which recognizes "a tumor associated fibronectin isoform," "*e.g.*, as recognized by the MAb BC-1." (see, *e.g.*, the '289 patent at col. 8, lines 7-11). As was discussed above in relation to the Mariani reference, the BC-1 antibody recognizes domain 7 of fibronectin, <u>not</u> the ED-B domain.

As for the obviousness rejection, none of the references of record, taken separately or together, suggests or discloses that in the present context (*i.e.*, a conjugate comprising an antibody specific for ED-B), it would be desirable to generate a conjugate which comprises an antibody with a specific, <u>high affinity</u> for ED-B, let alone one with an affinity in the subnanomolar range. That is, they do not provide motivation to do so. The attached paper by Viti *et al.* [(1999). *Cancer Research* <u>59</u>, 347-352], whose authors overlap with the instant inventors, demonstrates the desirability of high affinity for the angiogenic properties of the antibody.

In view of the above amendments and arguments, the application is believed to be in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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